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(71) Applicant *(for all designated States except US):* CIBA-GEIGY AG [CH/CH]; Klybeckstrasse 141, CH-4002 Basle (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* LUKAS, Gerhard [DE/CH]; In den Wegscheiden 16, CH-4132 Muttenz (CH). RAMSTEIN, Henri [FR/FR]; Rue des Landes, F-68300 Rosenau (FR). KEMMETHMÜLLER, Hans, Stefan, J. [DE/DE]; Edith-Stein-Strasse 9, D-7800 Freiburg (DE). BÜSCHER, Gottfried [DE/CH]; Lohweg 8, CH-4054 Basle (CH).

(74) Common Representative: CIBA-GEIGY AG; Patentabteilung, Klybeckstrasse 141, CH-4002 Basle (CH).

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(54) Title: VETERINARY MEDICINAL ANTHELMINTIC PREPARATION CONTAINING NITROSCANATE

(57) Abstract

The present invention relates to a veterinary medicinal anthelmintic preparation for oral administration to productive livestock or domestic animals, which preparation contains the compound 1-isothiocyanato-4-(4-nitrophenoxy)benzene known as nitroscanate, and is formulated as follows: active drug 0.5 to 90 %; with a particle size of 0.1 to 100 µm; solid carrier 0 to 98 %; with a particle size of 100 µm to 3 mm; surfactant 0.1 to 10 %; antifoam 0.5 to 20 %; suspension stabiliser/disintegrator 0 to 5 %; protective coating/binder 0.1 to 10 %; wetting agent 1 to 10 % and filler 0 to 50 %. The novel preparation has substantial advantages over known nitroscanate preparations.

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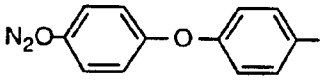
VETERINARY MEDICINAL ANTHELMINTIC PREPARATION CONTAINING NITROSCANATE

The present invention relates to a veterinary medicinal anthelmintic preparation for oral administration to productive livestock or domestic animals, which preparation contains the compound 1-isothiocyanato-4-(4-nitrophenoxy)benzene known as nitroscanate and which, owing to its specific formulation, is effective in substantially lower concentration than the known anthelmintic preparations containing the identical active drug and, in addition, can now also be readily used as broad spectrum anthelmintic for controlling helminth infestations in all productive livestock and domestic animals, including cats.

The novel veterinary medicinal anthelmintic preparation contains 1-isothiocyanato-4-(4-nitrophenoxy)benzene (nitroscanate) of formula  as active drug and is formulated as a granulate of the following composition, in which all percentages are by weight:

active drug	0.5	to	90 %;
with a particle size of	0.1	to	100 µm;
solid carrier	0	to	98 %;
with a particle size of	100 µm	to	3 mm;
surfactant	0.1	to	10 %;
antifoam	0.5	to	20 %;
suspension stabiliser/ disintegrator	0	to	5 %;
protective coating/binder	0.1	to	10 %;
wetting agent	1	to	10 % and
filler	0	to	50 %,

one adjunct of which formulation can have several functions and all components together do not exceed 100 %.

The antifoam, the suspension stabiliser/disintegrator, the filler and the carrier may be identical substances, but they can have different functions within the formulation. The

filler may typically have the properties of binder or disintegrator.

The term "adjunct" used throughout this specification shall be understood as meaning all formulation components except the active drug. Some adjuncts may have different functions and therefore fall into different groups of adjunct.

Depending on the mode of preparation, the granular formulation of this invention may have different embodiments. Preferred embodiments typically include extruder granulates and fluidised bed granulates. These last mentioned granulates are especially preferred within the scope of this invention.

A preferred extruder granulate contains 1-isothiocyanato-4-(4-nitrophenoxy)benzene (nitroscanate) as active drug and is in the form of a granular formulation of the following composition in which all precentages are by weight:

active drug	0.5	to	90 %;
with a particle size of	0.1	to	100 µm;
solid carrier	0		
surfactant	0.1	to	10 %;
disintegrator	0 %;		
suspension stabiliser/ disintegrator	0.5	to	20 %;
protective coating/binder	1	to	10 %;
wetting agent	1	to	5 % and
filler	0	to	50 %,

one adjunct of which formulation can have several functions and all components together do not exceed 100 %.

One of the preferred fluidised bed granulates contains 1-isothiocyanato-4-(4-nitrophenoxy)benzene (nitroscanate) as active drug and is in the form of a granular formulation of the following composition in which all percentages are by weight:

active drug	0.5	to	50 %;
with a particle size of	0.1	to	100 µm;
solid carrier	45	to	98 %;
with a particle size of	100 µm	to	3 mm;

surfactant	0.1	to	10 %;
suspension stabiliser/ disintegrator	0.01	to	1 %;
suspension stabiliser	0	to	5 %;
protective coating/binder	0.1	to	10 %;
wetting agent	0	to	2.5 %; and
filler	0	to	10 %,

one adjunct of which formulation can have several functions and all components together do not exceed 100 %.

Within the scope of the novel anthelmintic granular formulations, fluidised bed granulates are especially preferred which vary from the above particulars in one or other of the following features:

active drug	0.5	to	20 %;
with a particle size of	1	to	20 µm;
solid carrier	80	to	98 %;
with a particle size of	100 µm	to	1.0 mm;
surfactant	0.1	to	1 %;
suspension stabiliser/ disintegrator	0.1	to	1 %;
suspension stabiliser	0.1	to	2 %;
protective coating/binder	0.1	to	5 %;
wetting agent	0.8	to	1.2 %; and
filler	0	to	10 %,

one adjunct of which formulation can have several functions and all components together do not exceed 100 %.

1-Isothiocyanato-4-(4-nitrophenoxy)benzene known as nitroscanate is disclosed in DE-OS1 568 021 as a compound having anthelmintic properties. Its activity spectrum is thus known per se and embraces worms that are parasites of warm-blooded animals and are designated as helminths (nematodes, cestodes and trematodes). The target group specified in this publication comprises productive livestock and domestic animals, including cattle, pigs, horses, sheep, goats, dogs and cats. It is proposed to administer the drug in a single dose or repeatedly, the single dose being from 25-1000 mg/kg, depending on the species of animal.

Later, a number of scientific studies were published in which nitroscanate was administered for controlling worm species in different domestic animals, preferably dogs and cats.

In Research in Veterinary Science (1975) 19, 217-219, Gemmel et al. describe the effect of nitroscanate (10-20 µm) on *Echinococcus granulosus* and *Taenia hydatigena* infections. The drug was administered to the dogs in the form of capsules mixed with the feed. Successful results were obtained with dose rates of 250 mg/kg of bodyweight. At the same time, however, unacceptable side-effects such as vomiting, diarrhoea and tranquillising effects were also observed.

Two years later, the same authors again described in Research in Veterinary Science (1977) 22, 391-392 the effect of of nitroscanate (2-3 µm) on *Echinococcus granulosus* and *Taenia hydatigena* infections in dogs. In this case too the drug was administered to the dogs in the form of capsules. The authors recommended a single treatment of 64 mg/kg against *Echinococcus granulosus* and of 16 mg/kg against *Taenia hydatigena*. The authors again referred to undesirable side-effects such as vomiting.

In 1979, Gemmel et al. reported in Research in Veterinary Science (1979) 27, 255-257 on completely identical trials, except that the drug was this time administered to the dogs in tablet form. Depending on the worm species, statistically significant action was evidently achieved with single treatments of 32-250 mg/kg, whereas the efficiency of lower doses (2 mg/kg → 16 mg /kg) was statististically not significant. Here again the authors cited the earlier observed side-effects.

In the same year, Boray et al. reported in the Australian Veterinary Journal (1979) 55, 45-53 in their article "Nitroscanate a new broad spectrum anthelmintic against nematodes and cestodes of dogs and cats" on trials carried out with dogs and cats, and recommended the administration of nitroscanate at a dose rate of 25 to 200 mg/kg, depending on species of worm and host animal. These authors too reported on a number of undesirable side-effects, including vomiting, diarrhoea and loss of appetite.

It is therefore not entirely surprising that, in later publications, warnings on the use of nitroscanate are repeatedly found, especially as regards the use in cats, e.g:
R.K. Reinecke in 'Veterinary Helminthology' (Butterworths Durban/Pretoria) (1983),

page 169 "Never use nitroscanate in cats".
William C. Campbell and Robert S. Rew in 'Chemotherapy of Parasitic Diseases' (Plenum Press New York und London) (1986) Seite 413 "Nitroscanate is not recommended for the treatment of cats, as it has toxic side effects".
Trevor Turner in 'The Veterinary Record' August 8, 1987, 121, 121-123 declares on page 121 that Nitroscanat is "not suitable" for the treatment of cats.

The drug nitroscanate has been known to be an excellent broad spectrum anthelmintic but, as pointed out in the above dicsussion, there have been serious shortcomings of the dosage forms in which it has hitherto been administered and which have greatly restricted its use in veterinary practice.

The present invention has therefore for its object to provide a veterinary medicinal anthelmintic preparation in which the outstanding anthelmintic broad activity spectrum of nitroscanate is fully effective and which does not have the undesirable side-effects observed so far, and which can be used without problems for all productive livestock and domestic animals, including cats.

This object is achieved in surprisingly simple manner by the provision of the said novel preparation. It has now been found that an anthelmintic preparation containing nitroscanate and formulated as described at the outset in fact meets the required desiderata. The composition not only exhibits an activity in accord with the demands of practice, i.e. full activity against helminths in productive livestock and domestic animals in unusually low single doses of less than 25 (preferably 2 to 24) mg/kg, but also has a long shelf-life, a high acceptance in feed by the host animal, and is distinguished by the additional feature that the user virtually does not come in contact with the active drug owing to the protective film surrounding the particles. Furthermore, the administration of the novel preparation is extremely uncomplicated, as it is in granular form and can simply be mixed with the feed. In addition, the palatibility, i.e. the acceptance by the productive or domestic animal, is enhanced by the neutrally flavoured protective coating.

It is of course possible to add further active ingredients having the the same or different activity to the novel anthelmintic granular formulations conveniently for broadening the activity spectrum or for treating another disease. Thus it is possible to blend the novel preparations with other classes of anthelmintics, ectoparasiticides, growth promoters, fertility enhancing substances, vitamins, appetite stimulators or builders.

Suitable solid carriers for the novel anthelmintic granular formulations are the following carriers: very readily or readily water-soluble or water-dispersible crystalline carriers such as monovalent or polyvalent sugars, carbohydrates, inorganic salts and compounds, as well as polymers which are suitable for oral administration to a warm-blooded animal and have sufficient palatibility. Particularly suitable solid carriers are different sugars. Such suitable carrier materials are known in the art of vetinary galenics.

Within the scope of this invention, the term "sugar" will be understood as meaning all sugars that are in solid form at room temperature. These sugars may be selected from the class of the mono- and oligosaccharides such as mono-, di-, tri-, tetra- and pentasaccharides. In a preferred embodiment of the invention, the mono- and oligosaccharides are aldoses or ketoses. In a particularly preferred embodiment of the invention, the monosaccharides are aldopentoses, aldohexoses, ketopentoses or ketohexoses.
An aldopentose may typically be D-ribose, D-arabinose, D-xylose or D-lyxose; an aldohexose may typically be D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose or D-talose; a ketopentose may typically be D-ribulose or D-xylulose; a ketohexose may typically be D-psicose, D-fructose, D-sorbose or D-tagatose.
A disaccharide may typically be trehalose, maltose, isomaltose, cellobiose, gentibiose, saccharose or lactose. Saccharose is of very particular interest.
A trisaccharide may be exemplified by raffinose. Polysaccharides may typically be cellulose, starch, dextrans, glycogen, fructans, inulin, mannan, xylans and arabinans.

Suitable surfactants within the scope of this invention are neutral, amphoteric, cationic and anionic surfactants having a HLB value greater than 10 (HLB = hydrophilic-lipophilic balance). Particularly suitable surfactants include fatty acid glycerol polyglycol esters. Suitable surfactants are basically nonionic, cationic and/or anionic surfactants having good emulsifying, dispersing and wetting properties. Surfactants will also be understood as meaning mixtures of surfactants.
Suitable anionic surfactants may be so-called water-soluble soaps as well as water-soluble synthetic surfactants.

Suitable surfactants coming under the heading of "soaps" are the alkali metal salts, alkaline earth metal salts or the ammonium or substituted ammonium salts of higher

(C_{10}-C_{22})fatty acids, and also the sodium or potassium salts of oleic or stearic acid.

Frequently, however, so-called synthetic surfactants are used, preferably fatty sulfonates, fatty sulfates, sulfonated benzimidazole derivatives or alkylarylsulfonates.

The fatty sulfonates or sulfates are usually in the form of alkali metal salts, alkaline earth metal salts or unsubstituted or substituted ammonium salts and generally contain a C_8-C_{22}-alkyl radical which also includes the alkyl moiety of acyl radicals, e.g. the sodium or calcium salt of lignosulfonic acid, of dodecylsulfate, or of a mixture of fatty alcohol sulfates obtained from natural fatty acids. These compounds also comprise the salts of sulfated and sulfonated fatty alcohol/ethylene oxide adducts. The sulfonated benzimidazole derivatives preferably contain 2 sulfonic acid groups and one fatty acid radical containing about 8 to 22 carbon atoms. Examples of alkylarylsulfonates are the sodium, calcium or triethanolamine salts of dodecylbenzenesulfonic acid, dibutylnaphthalenesulfonic acid, or of a condensate of naphthalenesulfonic acid and formaldehyde. Also suitable are corresponding phosphates, e.g. salts of the phosphated adduct of p-nonylphenol with 4 to 14 moles of ethylene oxide; or phospholipids.

Non-ionic surfactants are preferably polyglycol ether derivatives of aliphatic or cycloaliphatic alcohols, or saturated or unsaturated fatty acids and alkylphenols, said derivatives containing 3 to 30 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenols. Further suitable non-ionic surfactants are the water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediaminopolypropylene glycol and alkylpolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethylene glycol ether groups and 10 to 100 propylene glycol ether groups. These compounds usually contain 1 to 5 ethylene glycol units per propylene glycol unit.

Representative examples of non-ionic surfactants are nonylphenolpolyethoxyethanols, castor oil thioxilate, polypropylene/polyethylene oxide adducts, tributylphenoxypolyethoxyethanol, polyethylene glycol and octylphenoxypolyethoxyethanol. Fatty acid esters of polyoxyethylene sorbitan, e.g. polyoxyethylene sorbitan trioleate, are also suitable non-ionic surfactants.

Cationic surfactants are preferably quaternary ammonium salts which contain, as N-substi-

tuent, at least one C_8-C_{22}alkyl radical and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl or hydroxy-lower alkyl radicals. The salts are preferably in the form of halides, methylsulfates or ethylsulfates, e.g. stearyltrimethylammonium chloride or benzyl bis(2-chloroethyl)ethylammonium bromide.

The surfactants customarily employed in the art of formulation are described e.g. in the following handbook:

"Mc Cutcheon's Detergents and Emulsifiers Annual", MC Publishing Corp., Ridgewood, NJ USA, 1988",

Antifoams which may suitably be used are typically silicone oils, polymethylsiloxanes, oleates or laurates. Suitable antifoams are described in the technical literature, inter alia in Dr. H. P. Fiedler: 'Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete' (Lexicon of adjuncts for Pharmacy, Cosmetics and Related Fields), 3rd edition, Editio Cantor, D-Aulendorf (1989). Especially preferred antifoams are polysiloxanes and, among these, methylpolysiloxane antifoams. Antifoams of this type are also termed 'Antifoam AF'.

Suspension stabilisers and disintegrators may typically be crosslinked alkali metal or alkaline earth metal salts of carboxymethyl cellulose, hydroxypropyl celluloses, polyvinyl pyrrolidone, preferably crosslinked polyvinyl pyrrolidone or polyethylene glycols.
A particularly preferred suspension stabiliser is microcrystalline cellulose.

Protective coatings and binders suitable for use in the practice of this invention are water-soluble film-formers such as cellulose ethers, water-soluble polymethacrylates and polyethylene glycols. Especially preferred binders are cellulose ethers. For the extruder granulates it is expedient to use macromolecular binders with good adhesive properties, typically hydroxypropyl celluloses, preferably hydroxypropylmethyl cellulose.

Suitable wetting agents are the polyglycol ether derivatives of aliphatic or cycloaliphatic alcohols, saturated or unsaturated fatty acids and alkyl phenols defined in the paragraph relating to surfactants. Particularly preferred wetting agents are, however, polyethylene glycols, most preferably polyethelene glycol 6000.

By normal temperature will be meant hereinafter a temperature in the range from 0 to

c. 50°C, preferably room temperature. The expression "elevated temperature" means a temperature above 50°C, especially a temperature above c. 55 to c. 100°C.

The component termed "filler" is used solely to adjust a specific final concentration. Basically all substances named as carriers may be used as filler, although, in contradistinction to the carrier, the particle size of the filler is not a critical parameter.

If it is desired to provide the novel granular formulation in the form of a fluidised bed granulate, it will be prepared by carrying out the following steps at normal temperature (c. 55-100°C, preferably 15-35°C, preferably at room temperature):

1. grinding nitroscanate to a particle size in the range from 0.1 to 100 µm;

2. converting the ground nitroscanate into a spray suspension by suspending it in a mixture of demineralised water, a suitable surfactant or mixture of surfactants, one or more than one film-former and one or more than one optional suspension stabiliser:

3. spraying a suitable solid carrier material at elevated temperature, typically in a fluidised bed dryer, with the spray suspension;

4. preparing a coating solution by mixing demineralised water and one or more than one film-former, with or without additional adjuncts;

5. coating a granular formulation obtainable in step 3 with a coating solution obtainable in step 4, conveniently in a fluidised bed dryer, at elevated temperature (c. 50-100°C, preferably 70-90°C);

6. isolating the dried and coated fluidised bed granular formulation.

If it is desired to provide the granular formulation in the form of an extruder granulate, it is prepared by carrying out the following steps at normal temperature (c. 0-50°C, preferably 15-35°C, preferably at room temperature):

1. grinding nitroscanate to a particle size in the range from 0.1 to 100 µm;

2. blending the finely ground nitroscanate with a disintegrator, a wetting agent and a

binder;

3. making the resultant mixture into a paste with a solution or dispersion of one or more than one surfactant in demineralised water;

4. extruding the moist paste to form cylindrical pellets through suitably dimensioned orifices, typically using rams or roll mills;

5. preparing a coating solution by mixing demineralised water and one or more than one film-formers, with or without additional adjuncts;

6. coating a granular formulation obtainable in step 4 with a coating solution obtainable in step 5, conveniently in a fluidised bed sprayer, at elevated temperature; and

7. isolating the dried and coated extruder granular formulation.

Preparation of the granulates

Example 1: Preparation of 2 kg of novel fluidised bed granulate

The drug nitroscanate is comminuted in a suitable grinding apparatus, most suitably an air jet mill. The grinding operation is controlled such that the desired particle size of 0.1 to 100 µm is attained. To prepare the spray suspension, 10.0 g of polyoxyethlated hydrogenated castor oil are dissolved in 700 g of demineralised water, then 20.0 g of polyethylene glycol 6000 are added, followed by the addition of 2.0 g of antifoam emulsion, and 200 g of the finely ground nitroscanate are suspended therein. A dispersing unit can be used for better dispersion of the ingredients. The supension is deaerated by applying a vacuum. With constant stirring, 20.0 g of microcrystalline cellulose are added, followed by the addition of 50.0 g of hydroxypropylmethyl cellulose. During this addition it is advantageous to prevent air from being stirred in. To prepare the coating solution, 50 g of hydroxypropylmethyl cellulose are stirred into 400 g of demineralised water and dissolved by stirring.

1648 g of sugar are charged to a fluidised bed sprayer and preheated to 50-80°C with warm air. After the desired temperature has been reached, the spray suspension is sprayed by a pump through a nozzle on to the fluidised carrier material. The flow of air is so

chosen that a uniform turbulent fluidised bed is obtained. Suitable nozzles are typically monofluid or two-fluid nozzles. Two-fluid nozzles are especially suitable. The optimum pumping rate and the further optimum machine parameters are each determined for the respective apparatus employed. A possible machine setting is:

air flow	$30m^3/h$
air flow tempera-ture	60°C
exhaust air temperature	40°C

After application of the spray suspension, the coating solution is sprayed on to the particles in the same manner. After the spraying operation, the granulate is dried in a stream of warm air.

Example 2: Preparation of 2 kg of the novel extruder granulate

The drug nitroscanate is comminuted in a suitable grinding apparatus, most suitably an air jet mill. The grinding operation is controlled such that the desired particle size of 0.1 to 100 µm is attained.
180 g of the comminuted drug are thoroughly mixed with 70 g of microcrystalline cellulose, 50 g of hydroxypropylmethyl cellulose and 20 g of polyethylene glycol 6000. Mixing can conveniently be effected in a ploughshare mixer.

10 g of polyoxyethlated hydrogenated castor oil are dissolved in 460 g of demineralised water. The drug/adjunct mixture is wetted with the resultant solution. This wetted mixture is then passed through an extruder with a c.1 mm orifice. This operation can be repeated a number of times for further compaction of the granulate.

To prepare the coating solution, 50 g of hydroxypropylmethyl cellulose are stirred into 450 g of demineralised water and dissolved by stirring. The cylindrical pellets obtained by extrusion are preheated to a temperature of c.50-80°C in a fluidised bed apparatus with warm air. After the desired temperature has been reached, the coating solution is sprayed on to the fluidised extruder granulate through a nozzle under the conditions described in Example 1. Finally, the coated extruder granulate is dried, preferably in a stream of warm air.

Examples of novel fluidised bed granulates

Example G1:

nitroscanate (2-20 µm)	10.0 g
sugar	82.4 g
polyethylene glycol 6000 vet	1.0 g
hydrogenated castor oil, polyoxyethylated	0.5 g
methylpolysiloxane emulsion	0.1 g
microcrystalline cellulose	1.0 g
hydroxypropylmethyl cellulose	5.0 g

Example G2:

nitroscanate (2-20 µm)	10.0 g
lactose, crystalline	81.1 g
polyoxyethylated sorbitan laurate	0.7 g
methylpolysiloxane emulsion	0.2 g
microcrystalline cellulose	1.5 g
hydroxypropylmethyl cellulose	5.5 g

Examples of novel extruder granulates

Example G3:

nitroscanate (2-20 µm)	1 800.0 g
microcrystalline cellulose	70.0 g
hydroxypropylmethyl cellulose	100.0 g
polyethylene glycol 6000 vet	20.0 g
hydrogenated castor oil, polyoxyethylated	10.0 g

Biological Examples for determining efficiency and tolerance

Example B1: Treatment of cats naturally infected with Toxocara cati (roundworm of cats)

20 cats naturally infected with Toxocara cati were divided into 4 groups. The granulate was given to each group of 5 cats with the feed at dose rates of 15 mg/kg, 10 mg/kg or 5 mg/kg of nitroscanate, or the group was untreated. After 1 week, a count was made of the number of worms in the intestinal tract of the cats. During the entire assay, the cats were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated cats was reduced by a specific percentage which was dose-dependent.

dose (mg/kg)	15	10	5
efficiency (%)	100	98	86

In the entire time after the treatment, no clinical symptoms were observed that would indicate a side-effect of the treatment.

Example B2: Treatment of cats artifically infected with Taenia taeniaeformis (tapeworm of cat)

35 cats artifically infected with Taenia taeniaeformis were divided into 4 groups. The granulate was given to each group of cats with the feed at dose rates of 15 mg/kg (4 cats), 10 mg/kg (9 cats) or 5 mg/kg (8 cats) of nitroscanate. 14 cats were untreated. After 5 days, a count was made of the number of worms that had survived the treatment. During the entire assay, the cats were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated cats was reduced by a specific percentage which was dose-dependent.

dose (mg/kg)	15	10	5
efficiency (%)	100	95	79

In the entire time after the treatment, no clinical symptoms were observed that would

indicate a side-effect of the treatment.

Example B3: Treatment of dogs naturally infected with several worm species (tapeworm, hookworm, roundworm)

15 dogs naturally infected with Taenia sp, Ancylostoma caninum and Toxocara canis were divided into 3 groups. The granulate was given to each group of 5 dogs with the feed at dose rates of 10 mg/kg or 5 mg/kg of nitroscanate, or the group was untreated. After 1 week, a count was made of the number of worms in the intestinal tract of the dogs. During the entire assay, the dogs were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated dogs was reduced by a specific percentage which was dose-dependent.

Dose (mg/kg)	Efficiency (%)		
(Worm species ⇒)	Taenia	Ancylostoma	Toxocara
5	20	98	77
10	91	100	100

In the entire time after the treatment, no clinical symptoms were observed that would indicate a side-effect of the treatment.

Example B4: Treatment of dogs naturally infected with several worm species tapeworm, hookworm, roundworm)

15 dogs naturally infected with Taenia sp, Ancylostoma caninum and Toxocara canis were divided into 3 groups. The granulate was given to each group of 5 dogs with the feed at dose rates of 10 mg/kg or 5 mg/kg of nitroscanate, or the group was untreated. After 1 week, a count was made of the number of worms in the intestinal tract of the dogs. During the entire assay, the dogs were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated dogs was reduced by a specific percentage which was dose-dependent.

Dose (mg/kg)	Efficiency (%)		
(Worm species ⇒)	Taenia	Ancylostoma	Toxocara
5	88	100	74
10	100	100	98

In the entire time after the treatment, no clinical symptoms were observed that would indicate a side-effect of the treatment.

Example B5: Treatment of dogs naturally infected with Ancylostoma caninum (dog hookworm)

10 dogs naturally infected with Ancylostoma caninum were divided into 2 groups. The granulate was given to each group of 5 dogs with the feed at a dose of 10 mg/kg of nitroscanate, or the group was untreated. After 1 week, a count was made of the number of worms in the intestinal tract of the dogs. During the entire assay, the dogs were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated dogs was reduced by 93 %.

In the entire time after the treatment, no clinical symptoms were observed that would indicate a side-effect of the treatment.

Example B6: Treatment of dogs naturally infected with Dipylidium caninum (dog tapeworm)

10 dogs naturally infected with Dipylidium caninum were divided into 2 groups. The granulate was given to each group of 5 dogs with the feed at a dose of 5 mg/kg of nitroscanate, or the group was untreated. After 1 week, a count was made of the number of worms in the intestinal tract of the dogs. During the entire assay, the dogs were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated dogs was reduced by 92 %.

In the entire time after the treatment, no clinical symptoms were observed that would indicate a side-effect of the treatment.

Example B7: Treatment of dogs naturally infected with Dipylidium caninum (dipyladiasis)

15 dogs naturally infected with Dipylidium caninum were divided into 2 groups. The granulate was given to a group of 4 dogs with the feed at a dose of 15 mg/kg of nitroscanate and 11 dogs were untreated. After 1 week, a count was made of the number of worms in the intestinal tract of the dogs. During the entire assay, the dogs were observed to record any side-effects of the treatment.

Compared with the untreated control, worm infestation in the treated dogs was reduced by 98 %.

In the entire time after the treatment, no clinical symptoms were observed that would indicate a side-effect of the treatment.

What is claimed is:

1. A veterinary medicinal anthelmintic preparation which contains 1-isothiocyanato-4-(4-nitrophenoxy)benzene (nitroscanate) as active drug, which preparation is formulated as a granulate and has the following composition:

active drug	0.5	to	90 %;
with a particle size of	0.1	to	100 µm;
solid carrier	0	to	98 %;
with a particle size of	100 µm	to	3 mm;
surfactant	0.1	to	10 %;
antifoam	0.5	to	20 %;
suspension stabiliser/ disintegrator	0	to	5 %;
protective coating/binder	0.1	to	10 %;
wetting agent	1	to	10 % and
filler	0	to	50 %,

such that all components together do not exceed 100 %.

2. A veterinary medicinal anthelmintic preparation according to claim 1 which is formulated as an extruder granulate and has the following composition:

active drug	0.5	to	90 %;
with a particle size of	0.1	to	100 µm;
solid carrier	0		
surfactant	0.1	to	10 %;
disintegrator	0 %;		
suspension stabiliser/ disintegrator	0.5	to	20 %;
protective coating/binder	1	to	10 %;
wetting agent	1	to	5 % and
filler	0	to	50 %,

such that all components together do not exceed 100 %.

3. A veterinary medicinal anthelmintic preparation according to claim 1 which is

formulated as a fluidised bed granulate and has the following composition:

active drug	0.5	to	50 %;
with a particle size of	0.1	to	100 µm;
solid carrier	45	to	98 %;
with a particle size of	100 µm	to	3 mm;
surfactant	0.1	to	10 %;
suspension stabiliser/ disintegrator	0.01	to	1 %;
suspension stabiliser	0	to	5 %;
protective coating/binder	0.1	to	10 %;
wetting agent	0	to	2.5 %; and
filler	0	to	10 %,

such that all components together do not exceed 100 %.

4. A veterinary medicinal anthelmintic preparation according to claim 3 which is formulated as a fluidised bed granulate and has the following composition:

active drug	0.5	to	20 %;
with a particle size of	1	to	20 µm;
solid carrier	80	to	98 %;
with a particle size of	100 µm	to	1.0 mm;
surfactant	0.1	to	1 %;
suspension stabiliser/ disintegrator	0.1	to	1 %;
suspension stabiliser	0.1	to	2 %;
protective coating/binder	0.1	to	5 %;
wetting agent	0.8	to	1.2 %; and
filler	0	to	10 %,

such that all components together do not exceed 100 %.

5. Use of 1-isothiocyano-4-(4-nitrophenoxy)benzene (nitroscanate) for the preparation of a granulate as claimed in any one of claims 1 to 4 for controlling helminths in productive livestock and domestic animals.

6. Use of 1-isothiocyano-4-(4-nitrophenoxy)benzene (nitroscanate) according to claim 5

for the preparation of a granulate for controlling helminths in productive livestock and domestic animals, said granulate being an extruder granulate.

7. Use of 1-isothiocyano-4-(4-nitrophenoxy)benzene (nitroscanate) according to claim 6 for the preparation of a granulate for controlling helminths in productive livestock and domestic animals, said granulate being an extruder granulate of the composition as indicated in claim 2.

8. Use of 1-isothiocyano-4-(4-nitrophenoxy)benzene (nitroscanate) according to claim 5 for the preparation of a granulate for controlling helminths in productive livestock and domestic animals, said granulate being a fluidised bed granulate.

9. Use of 1-isothiocyano-4-(4-nitrophenoxy)benzene (nitroscanate) according to claim 8 for the preparation of a granulate for controlling helminths in productive livestock and domestic animals, said granulate being a fluidised bed granulate of the composition as indicated in either claim 3 or claim 4.

10. Use of a granulate as claimed in any one of claims 1 to 4 for controlling helminths in productive livestock and domestic animals.

11. A process for the preparation of a granulate as claimed in claim 1 containing 1-isothiocyano-4-(4-nitrophenoxy)benzene (nitroscanate) for controlling helminths in productive livestock and domestic animals, which granulate is prepared in the form of (A) a fluidised bed granulate by carrying out the following steps at normal temperature:

1. grinding nitroscanate to a particle size in the range from 0.1 to 100 μm;
2. converting the ground nitroscanate into a spray suspension by suspending it in a mixture of demineralised water, a suitable surfactant or mixture of surfactants, one or more than one film-former and one or more than one optional suspension stabiliser:
3. spraying a suitable solid carrier material at elevated temperature, preferably in a fluidised bed sprayer, with the spray suspension;
4. preparing a coating solution by mixing demineralised water and one or more than one film-formers, with or without additional adjuncts;
5. coating a granular formulation obtainable in step 3 with a coating solution obtainable in step 4, preferably in a fluidised bed sprayer, at elevated temperature (c. 50-100°C, preferably 70-90°C);

6. isolating the dried and coated fluidised bed granulate;
and (B) as an extruder granulate by carrying out the following steps at normal temperature:
1. grinding nitroscanate to a particle size in the range from 0.1 to 100 μm;
2. blending the finely ground nitroscanate with a disintegrator, a wetting agent and a binder;
3. making the resultant mixture into a paste with a solution or dispersion of one or more than one surfactant in demineralised water;
4. extruding the moist paste to form cylindrical pellets through suitably dimensioned orifices;
5. preparing a coating solution by mixing demineralised water and one or more than one film-formers, with or without additional adjuncts;
6. coating a granular formulation obtainable in step 4 with a coating solution obtainable in step 5, preferably in a fluidised bed sprayer, at elevated temperature; and
7. isolating the dried and coated extruder granulate.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/01739

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/26; A61K9/16; A61K9/50

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	FR,A,1 491 477 (AGRIPAT S.A.) 11 August 1967 cited in the application see claim 1 see page 5,right column,lines 1-27	1-11
A	GB,A,2 224 933 (MERCK) 23 May 1990 see claims see page 5, line 31 - line 35 see page 6, line 10 - line 23 see page 7, line 22 - line 25	1-11

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 SEPTEMBER 1993	07. 10. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCARPONI U.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/01739

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	US,A,4 117 156 (W.LOEWE) 26 September 1978 see claims see column 7, line 28 - line 40 see column 8, line 5 - line 19 see column 9, line 24 - line 32 see example 2 ---	1-11
A	CHEMICAL ABSTRACTS, vol. 92, no. 8 Columbus, Ohio, US; abstract no. 64644v, cited in the application see abstract & RES.VET.SCI. vol. 27, no. 2, 1979, pages 255 - 257 M.A.GEMMEL ET AL. 'The effect of nitroscanate tablets on Echinococcus Granulosus and Taenia Hydatigena infections in dogs' -----	1-11

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9301739
SA 76575

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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GB-A-2224933	23-05-90	None		
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		AU-A-	1596176	19-01-78
		DE-A,C	2631524	03-02-77
		FR-A,B	2317920	11-02-77
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82